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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,714	FLEGEL ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Thee* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *13 and 15-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-12,14,48,50 and 51* is/are rejected.

7)☒ Claim(s) *6, 8 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/8/03 has been entered.

2. Claims 1-51 are pending.

3. Claims 13, and 15-47 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-12, 14, and 48-51 are being acted upon in this Office Action.

1. The disclosure stands objected to because of the following informality: (1) the arrangement of the specification. See Arrangement of the Specification in Action mailed 9/25/01. Appropriate correction is required.

2. The drawings, filed 10/4/00, stand not approved.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5, 7, 9-12, 14, 48, and 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) an isolated nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation in its transmembrane and/or intracellular regions as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41 wherein the missense mutation occurs in nucleotide position 8 from C to G, nucleotide position 29 from G to A, nucleotide position 48 from G to C, nucleotide position 340 from C to T, nucleotide position

446 from C to A, nucleotide position 544 from T to A, nucleotide position 594 from A to T, nucleotide position 602 from C to G, nucleotide position 658 from T to C, nucleotide position 667 from T to G, nucleotide position 809 from T to G, nucleotide position 819 from G to A, nucleotide position 826 from G to C, nucleotide position 830 from G to A, nucleotide position 845 from G to A, nucleotide position 880 from G to C, nucleotide position 885 from G to T, nucleotide position 919 from G to A, nucleotide position 1016 from G to A, nucleotide position 1154 from G to C and nucleotide position 1177 from T to C of SEQ ID NO: 41 or a combination thereof, (2) An isolated nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation in SEQ ID NO: 41 wherein the missense mutation results in amino acid substitution in the Rhesus D antigen at position selected from the group consisting of 3 from Ser to Cys, 10 from Arg to Gln, 16 from Trp to Cys, 114 from Arg to Trp, 149 from Ala to Asp, 182 from Ser to Thr, 198 from Lys to Asn, 201 from Thr to Arg, 220 from Trp to Arg, 223 from Phe to Val, 270 from Val to Gly, 276 from Ala to Pro, 277 from Gly to Glu, 282 from Gly to Asp, 294 from Ala to Pro, 295 from Met to Ile, 307 from Gly to Arg, 339 from Gly to Glu, 385 from Gly to Ala and 383 from Trp to Arg with the proviso that said D antigen does not carry not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine, (3) a vector comprising the nucleic acid molecule mentioned above, (4) a host cell transformed with said vector, (5) a method of producing a Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced for diagnosis and screening assays, and (6) an oligonucleotide selected from the group consisting of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 that hybridize under 0.1X SSC, 0.1% SDS at 65°C hybridization and washing conditions to a portion of SEQ ID NO: 41 comprising said at least one missense mutations or to the complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2 for screening missense mutation in *RHD* gene, **does not** reasonably provide enablement for (1) *any* nucleic acid molecule encoding any human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one of *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in its transmembrane and/or intracellular regions, (2) *any* nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule (a) carrying at least one any missense

mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid positions such as the ones recited in claim 2 or carrying *any* gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene, (3) the nucleic acid molecule encoding *any* human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one of *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in its transmembrane and/or intracellular regions wherein said missense mutation causes *any* amino acid substitution in position such as the ones recited in claim 3 or the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule (a) carrying at least one of *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid positions such as the ones recited in claim 2 or carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said missense mutation causes *any* amino acid substitution in position such as the ones recited in claim 3, (4) the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said missense mutation causes *any* amino acid substitution in position such as the ones recited in claim 4, (5) the nucleic acid molecule encoding any human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in its transmembrane and/or intracellular regions wherein said missense mutation occurs in nucleotide position such as the ones recited in claim 5, the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one any missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid positions such as the ones recited in claim 2 or carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said missense mutation occurs in nucleotide position such as the ones recited in claim 5, (6) the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said missense mutation in position such as the ones recited in claim 6, (7) the nucleic acid molecule encoding a human Rhesus D antigen

contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein the combination of substitution such as the ones recited in claim 7, (8) the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said combination of missense mutations "comprises" position 554, 594, and 602 and is T to A at position 544, A to T at position 594 and C to G at position 602 or "comprises" positions 602, 677, and 819 and is C to G at position 602, T to G at position 667 and G to A at position 819 or "comprises" positions 48, 602, 667 and 819 and is G to C at position 48, C to G at position 602, T to G at position 667 and G to A at position 819, (9) the nucleic acid molecules mentioned above wherein said molecule is any mRNA, or any genomic DNA, (10) A vector comprising any nucleic acid molecule mentioned above, (11) any host cell transformed with said vector, (11) A method of producing any Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced, and (12) *any* oligonucleotide, *any* oliglonucleotide 12 to 50 or *any* oligonucleotide 15 to 24 nucleotides in length hybridizing under 0.1X SSC, 0.01%SSC, 0.1% SDS at 65°C hybridization and washing conditions to any portion of the nucleic acid mentioned above for any purpose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 12.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes a wild type human Rhesus D antigen. The specification further discloses one or more missense mutations in SEQ ID NO: 41 that contribute to weak D phenotype wherein the missense

mutations occurs in nucleotide position 8 is from C to G, position 29 from G to A, position 48 from G to C, position 340 from C to T, position 446 from C to A, position 544 from T to A, position 594 from A to T, position 602 from C to G, in position 658 from T to C, position 667 from T to G, position 809 from T to G, position from 819 from G to A, position 826 from G to C, position 830 from G to A, position 845 from G to A, position 880 from G to C, position 885 from G to T, position 919 from G to A, position 1016 from G to A, position 1154 from G to C, and position 1177 from T to C of SEQ ID NO: 41 or in a combination of said position. An isolated nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one missense mutation in SEQ ID NO: 41 wherein the missense mutation results in amino acid substitution in the Rhesus D antigen at position selected from the group consisting of 3 from Ser to Cys, 10 from Arg to Gln, 16 from Trp to Cys, 114 from Arg to Trp, 149 from Ala to Asp, 182 from Ser to Thr, 198 from Lys to Asn, 201 from Thr to Arg, 220 from Trp to Arg, 223 from Phe to Val, 270 from Val to Gly, 276 from Ala to Pro, 277 from Gly to Glu, 282 from Gly to Asp, 294 from Ala to Pro, 295 from Met to Ile, 307 from Gly to Arg, 339 from Gly to Glu, 385 from Gly to Ala and 383 from Trp to Arg with the proviso that said D antigen does not carry not carry a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine, (3) a vector comprising the nucleic acid molecule mentioned above, (4) a host cell transformed with said vector, (5) a method of producing a Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced for diagnosis and screening assays, and (6) an oligonucleotide selected from the group consisting of SEQ ID NOS: 3-4, 7, 16-18, 20, 23, 25-26, 29-30 and 39-40 that hybridize under 0.1X SSC, 0.1% SDS at 65°C hybridization and washing conditions to a portion of SEQ ID NO: 41 comprising said at least one missense mutations or to the complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2 for screening missense mutation in *RHD* gene.

Claims 1-3 encompass any base change in any nucleic acid molecule such as mRNA and genomic DNA and any amino acid substitution in positions such as 2-16, 114-149, 179-225 or/and 267 to 397 and any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene.

With the exception of the specific nucleic acid molecules encoding the specific missense mutations in the human Rhesus D antigen mentioned above, there is insufficient guidance and

working example as to which base change or substitution (claim 1) in a codon that causes insertion of a different amino acid (missense mutation) in the transmembrane and/or intracellular regions of the human Rhesus D antigen encoded by SEQ ID No 41 and whether the resulting nucleic acid molecule maintains its structure and function as SEQ ID NO: 41. There is also insufficient guidance and working example as to which amino acid in amino acid positions such as the ones recited in claim 2 be substitute for which undisclosed amino acid (claim 2) the would maintain the same structure and function as SEQ ID NO: 41 or that would result in weak Rhesus D phenotypes. As to gene conversion involving exons 6 to 9, the specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes the wild type human Rhesus D antigen. There is insufficient guidance as to the nucleic acid molecule that corresponds to exons 6 to 9 of human Rhesus D antigen and exons 6 to 9 of the "RHCE gene", much less which base change, the corresponding amino acid substitution in the undisclosed nucleic acid molecule for any purpose. Even if the missense mutation is limited to the specific amino acid position such as the ones recited in claim 3 or the specific amino acid substitution such as the ones recited in claim 4, it is not clear if those positions and/or amino acid substitution are applicable to gene conversion involving exons 6 to 9 when replaced by the corresponding exons of the RHCE gene. Further, there is insufficient guidance as to which undisclosed amino acid to be substituted at those positions such as the ones recited in claim 3. Further, there is insufficient guidance and working example as to which undisclosed nucleotide, the corresponding amino acids to be substitute at nucleotide positions such as the ones recited in claim 5, much less about the combination of said positions and whether the resulting nucleic acid molecule maintains its structure and function that contribute to human Rhesus D antigen, in turn, would be useful for diagnosis.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Skolnick *et al* teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). Given the indefinite number of missense mutation in the nucleic acid

molecule, it is unpredictable which undisclosed "nucleic acid molecule" contributes to weak D phenotype and would be useful for screening the presence of one or more missense mutation in Rh D antigens of blood of donor and recipient. Since the nucleic acid molecule is not enable, it follows that the vector and host cell comprising said undisclosed nucleic acid molecule is not enable. It also follows that any oligonucleotide hybridizing to any undisclosed nucleic acid molecule carrying any missense mutation is not enabled.

With regard to "oligonucleotide", the claim encompasses any random sequence such as any oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length. There is inadequate written description about the structure without the nucleotide sequence. Even if the oligonucleotide is limited to 12 to 50 or 15 to 24 nucleotides in length that would hybridize under the condition such as 0.1X SSC, 0.1% SDS at 65°C, it is not clear if it would specifically detects the specific missense mutation or gene conversion involving exons 6 to 9 that contributes to weak D phenotype, in turn, would be useful for screening and diagnosis.

The state of the prior art as exemplified by Wallace *et al* (of record) and Sambrook *et al* (of record) is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Even if the probe is a 20mer, the total number of hits in a database search was 143,797,728, which suggest that some of the probes encompassed by the claims would not preferentially hybridize to a "nucleic acid molecule" that encodes a Rhesus D antigen. Since the undisclosed oligonucleotide would not hybridize specifically to the undisclosed nucleic acid molecule that encodes a Rhesus D antigen contributing to or indicative of the weak D phenotype, it follows that the oligonucleotide would not specifically hybridize to the "complementary portion thereof" or any region involving the breakpoint of the gene conversion as recited in claim 14. Since the oligonucleotide is not enabled, it follows that any kit comprising said oligonucleotide is not enable.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 9/8/03 have been fully considered but are not found persuasive.

Applicants' position is that claims 1 and 2 have been amended to recite that the nucleotide molecule carrying at least one missense mutation is as compared to the wild type Rhesus D antigen set forth in SEQ ID INO: 41.

However, the nucleic acid molecule in amended claims 1 and 2 still encompass any missense mutation. There is insufficient guidance and working example as to which base change or substitution (claim 1) in which codon that causes insertion of a different amino acid (missense mutation) in the transmembrane and/or intracellular regions of the human Rhesus D antigen encoded by SEQ ID No 41 and whether the resulting nucleic acid molecule maintains its structure and function as SEQ ID NO: 41 or contributes to weak Rhesus D phenotype. There is also insufficient guidance and working example as to which amino acid in amino acid positions such as the ones recited in claim 2 be substitute for which undisclosed amino acid (claim 2) the would maintain the same structure and function as SEQ ID NO: 41 or that that result in weak Rhesus D phenotypes. As to gene conversion involving exons 6 to 9, the specification discloses only one polynucleotide of SEQ ID NO: 41 that encodes the wild type human Rhesus D antigen. There is insufficient guidance as to the nucleic acid molecule that corresponds to exons 6 to 9 of human Rhesus D antigen and exons 6 to 9 of the "RHCE gene", much less which base change, and the corresponding amino acid substitution in the undisclosed nucleic acid molecule for any purpose. Even if the missense mutation is limited to the specific amino acid position such as the ones recited in claim 3 or the specific amino acid substitution such as the ones recited in claim 4, it is not clear if those positions and/or amino acid substitution are applicable to gene conversion involving exons 6 to 9 when replaced by the corresponding exons of the RHCE gene. Further, there is insufficient guidance as to which undisclosed amino acid to be substituted at those positions recited in claim 3. Further, there is insufficient guidance and working example as to which undisclosed nucleotide, the corresponding amino acids to be substitute at nucleotide positions such as the ones recited in claim 5, much less about the combination of said positions and whether the resulting nucleic acid molecule maintains its structure and function that contribute to human Rhesus D antigen, in turn, would be useful for diagnosis.

5. Claims 1-5, 7, 9-12, 14, 48, and 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* nucleic acid molecule encoding any human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in its transmembrane and/or intracellular regions, (2) *any* nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule (a) carrying at least one any missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid positions such as the ones recited in claim 2 or carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene, (3) the nucleic acid molecule encoding any human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in its transmembrane and/or intracellular regions wherein said missense mutation causes *any* amino acid substitution in position such as the ones recited in claim 3 or the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule (a) carrying at least one any missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid positions such as the ones recited in claim 2 or carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said missense mutation causes *any* amino acid substitution in position such as the ones recited in claim 3, (4) the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said missense mutation causes *any* amino acid substitution in position such as the ones recited in claim 4, (5) the nucleic acid molecule encoding any human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one *any* missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in its transmembrane and/or intracellular regions wherein said missense mutation occurs in nucleotide position such as the ones recited in

claim 5, the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying at least one any missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid positions such as the ones recited in claim 2 or carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said missense mutation occurs in nucleotide position such as the ones recited in claim 5, (6) the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said missense mutation in position such as the ones recited in claim 6, (7) the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein the combination of substitution such as the ones recited in claim 7, (8) the nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype, said nucleic acid molecule carrying any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene wherein said combination of missense mutations "comprises" position 554, 594, and 602 and is T to A at position 544, A to T at position 594 and C to G at position 602 or "comprises" positions 602, 677, and 819 and is C to G at position 602, T to G at position 667 and G to A at position 819 or "comprises" positions 48, 602, 667 and 819 and is G to C at position 48, C to G at position 602, T to G at position 667 and G to A at position 819, (9) the nucleic acid molecules mentioned above wherein said molecule is any mRNA, or any genomic DNA, (10) A vector comprising any nucleic acid molecule mentioned above, (11) any host cell transformed with said vector, (11) A method of producing any Rhesus D antigen contributing to the weak D phenotype comprising culturing said host cell under suitable conditions and isolating the Rhesus D antigen produced, and (12) *any* oligonucleotide, *any* oliglonucleotide 12 to 50 or *any* oligonucleotide 15 to 24 nucleotides in length hybridizing under 0.1X SSC, 0.01%SSC, 0.1% SDS at 65°C hybridization and washing conditions to any portion of the nucleic acid mentioned above for any purpose.

With the exception of the specific nucleic acid molecules encoding the specific missense mutations in the human Rhesus D antigen mentioned above, there is inadequate written description about which base change or substitution (claim 1) in which codon that causes

insertion of a different amino acid (missense mutation) in the transmembrane and/or intracellular regions of the human Rhesus D antigen encoded by SEQ ID No 41 and whether the resulting nucleic acid molecule is indicative of the weak Rhesus D phenotype. As to claim 2, there is inadequate written description about which undisclosed amino acid to be substituted in amino acid positions such as 2-16, 114-149, 179-225 or/and 267 to 397 as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 4 and the resulting nucleic acid molecule contributing to or indicative of the weak D phenotype or which undisclosed nucleic acid molecule that corresponds to exons 6 to 9 of human Rhesus D antigen and exons 6 to 9 of the "RHCE gene". The specification discloses only one nucleic acid molecule (SEQ ID NO: 41) that encodes a human Rhesus D antigen. There is inadequate written description about which undisclosed nucleic acid molecule corresponds to exons 6 to 9 of human Rhesus D antigen and which nucleic acid molecule corresponds to exons 6 to 9 of the RHCE gene. Even if the missense mutation is limited to the specific amino acid position such as the ones recited in claim 3 or the specific amino acid substitution such as the ones recited in claim 4, it is not clear if those positions and/or amino acid substitution are applicable to gene conversion involving exons 6 to 9 when replaced by the corresponding exons of the RHCE gene. Further, there is insufficient written description as to which undisclosed amino acid to be substituted at those positions such as the ones recited in claim 3 or which undisclosed nucleotide, the corresponding amino acids to be substitute at nucleotide positions such as the ones recited in claim 5. Let alone the resulting nucleic acid molecule maintains its structure and function that contribute to human Rhesus D antigen, in turn, would be useful for diagnosis.

With regard to "oligonucleotide", the claim encompasses any random sequence such as any oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length. There is inadequate written description about the structure (nucleotide sequence) of said oligonucleotide so long it is 12 to 50 or 15 to 24 nucleotides in length that would hybridize under the condition such as 0.1X SSC, 0.1% SDS at 65°C to any undisclosed nucleic acid molecule such as nucleic acid carrying a gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene that encodes a human Rhesus D antigen contributing to weak D phenotype, in turn, would be useful for screening and diagnosis. Since the oligonucleotide is not adequately describe, it follows that any kit comprising said "oligonucleotide" is not sufficient described. Given that the "nucleic acid molecule" is not adequately described, the complementary thereof and any region involving the breakpoint of the gene conversion are not adequately described for the same reasons

mentioned above. It is noted that though the claimed invention is directed to "nucleic acid molecule", the principle still holds for the amino acid encoded by said "nucleic acid molecule". Sine only one polynucleotide of SEQ ID NO: 41 that encodes a Rhesus D antigen is disclosed, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species nucleic acid molecule carrying any one missense mutation, and any combination of any nucleotide or amino acid position to describe the genus.

With regard to "oligonucleotide", the claim encompasses any random sequence such as any oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length. There is inadequate written description about the structure without the nucleotide sequence. Even if the oligonucleotide is limited to 12 to 50 or 15 to 24 nucleotides in length that would hybridize under the condition such as 0.1X SSC, 0.1% SDS at 65°C, it is not clear if it would specifically detects the specific missense mutation or gene conversion involving exons 6 to 9 that contributes to weak D phenotype, in turn, would be useful for screening and diagnosis. Given the indefinite number of oligonucleotide that may encompassed by the claim, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 9/8/03 have been fully considered but are not found persuasive.

Applicants' position is that claims 1 and 2 have been amended to recite that the nucleotide molecule carrying at least one missense mutation is as compared to the wild type Rhesus D antigen set forth in SEQ ID INO: 41.

However, the nucleic acid molecule in amended claims 1 and 2 still encompass any missense mutation. There is inadequate written description about which base change or substitution (claim 1) in which codon of SEQ ID NO: 41 that causes insertion of a different amino acid (missense mutation) in the transmembrane and/or intracellular regions of the human Rhesus D antigen and whether the resulting nucleic acid molecule encoding the polypeptide that is indicative of the weak D phenotype. As to claim 2, there is inadequate written description about which undisclosed amino acid to be substituted in amino acid positions such as 2-16, 114-149, 179-225 or/and 267 to 397 as compared to the wild type Rhesus D antigen set forth as SEQ

ID NO: 41 and whether the resulting nucleic acid molecule contributing to or indicative of the weak D phenotype. There is inadequate written description bout the undisclosed nucleic acid molecule that corresponds to exons 6 to 9 of human Rhesus D antigen and exons 6 to 9 of the "RHCE gene". The specification discloses only one nucleic acid molecule (EQ ID NO: 41) encoding a human Rhesus D antigen. Further, even if the missense mutation is limited to the specific amino acid position such as the ones recited in claim 3 or the specific amino acid substitution such as the ones recited in claim 4, it is not clear if those positions and/or amino acid substitution are applicable to gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene and whether the resulting nucleic acid molecule maintains its structure and function such as contributing to or indicative of weak D phenotype, in turn, would be useful for diagnosis.

With regard to "oligonucleotide", the claim encompasses any random sequence such as any oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length. There is inadequate written description about the structure without the nucleotide sequence. Even if the oligonucleotide is limited to 12 to 50 or 15 to 24 nucleotides in length that would hybridize under the condition such as 0.1X SSC, 0.1% SDS at 65°C, it is not clear if it would specifically detects the specific missense mutation or gene conversion involving exons 6 to 9 that contributes to weak D phenotype, in turn, would be useful for screening and diagnosis.

Flegel *et al* (PTO 1449) teach that specific detection of nucleotides at predetermined sequence positions require guidance and single primer pair such as oligonucleotides are not considered reliable and should not generally be applied for diagnostic purposes (See page 289, column 2, in particular). Since the structure of the oligonucleotide is not adequately describe, it follows that any kit comprising said "oligonucleotide" is not sufficient described. Given that the "nucleic acid molecule" is not adequately described, the complementary thereof and any region involving the breakpoint of the gene conversion are not adequately described for the same reasons as mentioned above. It is noted that though the claimed invention is directed to "nucleic acid molecule", the principle still holds for the amino acid encoded by said "nucleic acid molecule". Sine only one polynucleotide of SEQ ID NO: 41 that encodes a Rhesus D antigen is disclosed, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species nucleic acid molecule carrying any one missense mutation, and any combination of any nucleotide or amino acid position to describe the genus.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 2 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Rouillac *et al* (Am J Hematol 49(1): 87-8, May 1995; PTO 892).

Rouillac *et al* teach a polynucleotide that encodes a human Rhesus D antigen such as Rh40 carrying one missense mutation at nucleotide position 329 from T to C that results in amino acid substitution from leucine to proline substitution at position 110 which is within the 114-149 of the RhD polypeptide compared to the wild type sequence of the claimed SEQ ID NO: 41 (See abstract, in particular). The reference D antigen does not carry a single missense mutation leading to a substitution of phenylaline in amino acid position 223 by valine or of threonine in position 283 by isoleucine (See Fig 1, in particular). The reference polynucleotide is genomic DNA (See Materials and methods, in particular). Thus, the reference teachings anticipate the claimed invention.

8. Claims 1, 3, 4, 5, 9, 12, and 50-51 are rejected under 35 U.S.C. 102(a) as being anticipated by Legler *et al* (Transfusion 38(5): 434-40, May 1998; PTO 892).

Legler *et al* teach a polynucleotide that encodes a human Rhesus D antigen contributing to or indicative of the weak D phenotype that has at least one missense mutation as compared to the wild type Rhesus D antigen such as a point mutation at nucleotide 667 (T to G) that resulted in a Phe at amino acid position 223 to Val, Glu at position 233 to Gln and Val at 238 to Met) (See abstract, Figure 3, page 437, column 1, in particular). The reference missense mutations such as positions 223 and 238 are located in the intramembrane region of the reference RhD antigen. Legler et al further teach the reference polynucleotide carries a missense mutation at nucleotide 667 from T to G (See Figure 2, in particular). The reference polynucleotide is genomic DNA (See legend of Figure 2, Materials and methods, in particular). The reference further teaches various oligonucleotides that hybridize to a portion of the reference nucleic acid molecule comprising the reference missense mutation (See Table 1, page 435, in particular). The reference

oligonucleotides are 17 nucleotides in length which are within the claimed 12 to 50 or 15 to 24 nucleotides in length. Thus, the reference teachings anticipate the claimed invention.

9. Claims 2, 9, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Avent *et al* (Blood 89(7): 2568-77, April 1997; PTO 1449).

Avent *et al* teach a nucleic acid molecule encoding human Rhesus D antigen contributing to or indicative of weak D phenotype carrying a gene conversion involved exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene (See Figure 7, Fig 2, in particular). The reference further teaches oligonucleotides such as *RHD* specific intron 4 (antisense, primer A) and *RHD* specific primer B that hybridizes to a region involving breakpoint of the gene conversion or missense mutation of the reference nucleic acid (See 2569, Materials and Methods, in particular). The reference polynucleotide is genomic DNA (See Materials and methods, page 2569, in particular). Thus, the reference teachings anticipate the claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 2, and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rouillac *et al* (Am J Hematol 49(1): 87-8, May 1995; PTO 892) or Legler *et al* (Transfusion 38(5): 434-40, May 1998; PTO 892) or Avent *et al* (Blood 89(7): 2568-77, April 1997; PTO 1449) each in view of Sambrook *et al* (of record, *Molecular Cloning*, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17).

The teachings of Rouillac *et al*, Legler *et al* and Avent *et al* have been discussed supra.

The claimed invention in claim 10 differs from the teachings of the references only that a vector comprising the nucleic acid encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype in its transmembrane and/or intracellular regions as compared to the wild type Rhesus D antigen as set forth in SEQ ID NO: 41 or the nucleic acid molecule carrying at least one missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO: 41, in amino acid position 114-149 with the proviso that said D antigen does carry not a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine or carrying a gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene.

Sambrook *et al* teach cloning a cDNA into an expression vector, a process of transforming the expression vector into host cells, culturing the host cells under conditions in which the polypeptide is expressed and then recovering the polypeptide from the culture. Sambrook *et al* teach that it is desirable to use recombinant DNA techniques for the production of biologically active proteins in order to produce proteins of higher concentration and purity.

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce any Rhesus D antigen contributing to weak D phenotype by culturing host cell transformed with the vector comprising the polynucleotide taught by Rouillac *et al* or Legler *et al* or Avent *et al* and isolating the Rhesus D antigen as taught by Sambrook *et al and* Rouillac *et al* or Legler *et al* or Avent *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because there would be a higher yield of polypeptide with greater purity as taught by Sambrook *et al.*

13. Claims 1, 2, 14, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avent *et al* (Blood 89(7): 2568-77, April 1997; PTO 1449) in view of US Pat No. 6,200,802 (Filed Oct 1993, PTO 892).

The teachings of Rouillac *et al*, Legler *et al* and Avent *et al* have been discussed supra.

The claimed invention in claim 48 differs from the teachings of the references only that a kit comprising the oligonucleotide.

The '802 patent teaches a kit comprising oligonucleotide for screening assays (see column 33, lines 43-50, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the oligonucleotide in a kit as taught by the '802 patent with the oligonucleotide as taught by Avent *et al* and packing it in a kit for various screening assays as taught by the '802 patent with the expectation that a kit will allow for convenience and commercial expedience. From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references.

5. Claims 6, 8 and 49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

8. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

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